PAPERS AND ORIGINALS

Intravenous N-acetylcysteine: the treatment of choice for paracetamol poisoning

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Summary and conclusions

One hundred cases of severe paracetamol poisoning were treated with intravenous N-acetylcysteine (acetylcysteine). There was virtually complete protection against liver damage in 40 patients treated within eight hours after ingestion (mean maximum serum alanine transaminase activity 27 IU/l). Only one out of 62 patients treated within 10 hours developed severe liver damage compared with 33 out of 57 patients (58%) studied retrospectively who received supportive treatment alone. Early treatment with acetylcysteine also prevented renal impairment and death. The critical ingestion-treatment interval for complete protection against severe liver damage was eight hours. Efficacy diminished progressively thereafter, and treatment after 15 hours was completely ineffective.

Intravenous acetylcysteine was more effective than cysteamine and methionine and noticeably free of adverse effects. It is the treatment of choice for paracetamol poisoning.

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Introduction

Now that the biochemical mechanisms of paracetamol hepatotoxicity are understood[1] sulphydryl compounds such as cysteamine, L-methionine, and *N*-acetylcysteine (acetylcysteine) may be used successfully to treat severe paracetamol poisoning.[2-10] Nevertheless, the relative efficacy of these agents in protecting against liver damage, renal impairment, and death is uncertain and doubts have been raised about the safety of cysteamine and methionine.[2-8] Furthermore, cysteamine and methionine are not available commercially for intravenous administration. Our initial findings with intravenous acetylcysteine were encouraging,[4 5] and we describe here the results of treating 100 cases.

Patients and methods

Patients—Eighty-seven patients admitted on 100 occasions with severe paracetamol poisoning between December 1976 and May 1979 were treated with intravenous acetylcysteine. Their mean age was 33 years (range 13-82), and 33 were male. Those admitted on more than one occasion were considered as separate patients for each admission. Forty-eight patients claimed to have taken only paracetamol, 31 took it in combination with dextropropoxyphene as Distalgesic, and the remainder also took one or more other drugs, usually benzodiazepines or aspirin. All patients were admitted within 24 hours after ingestion and had plasma paracetamol concentrations above a treatment line joining plots of 200 mg/l at four hours and 30 mg/l at 15 hours on a semilogarithmic graph. More-severely poisoned patients with plasma paracetamol concentrations above a similar line joining 300 mg/l at four hours and 45 mg/l at 15 hours were defined as "high-risk" cases. Patients with values between these two lines were designated as an "intermediate-risk" group. When necessary the lines were extrapolated to 24 hours.

General management—Gastric aspiration and lavage were performed on patients admitted within four hours of ingestion and those in coma. Patients with persistent nausea and vomiting were given intravenous fluid replacement and antiemetics. Impending or established hepatic failure was treated conventionally. Twenty-one patients who took Distalgesic required naloxone—20 were in deep coma, and respiratory arrest had occurred in 10.

Treatment with acetylcysteine—Intravenous acetylcysteine was given in an initial dose of 150 mg/kg in 200 ml 5% dextrose over 15 minutes

followed by 50 mg/kg in 500 ml 5% dextrose over four hours and 100 mg/kg in one litre 5% dextrose over the next 16 hours (total dose 300 mg/kg in 20 hours). Roughly half of the patients were given Airbron, which is a 20% sterile aqueous solution of acetylcysteine for intrabronchial use. The remainder were given a similar solution specially prepared by the manufacturer for intravenous use.

Investigations—Initially, the pulse rate, blood pressure, temperature, and electrocardiogram (ECG) were monitored closely during administration of acetylcysteine. Full blood counts and estimations of prothrombin-time ratio, activities of serum aspartate transaminase (SGOT; serum AST) and serum alanine transaminase (SGPT; serum ALT), and plasma bilirubin, urea, creatinine, and electrolyte concentrations were usually performed on admission and daily for three to five days. Plasma paracetamol concentrations measured on admission[11] were confirmed by specific chromatographic methods.[12 13]

Assessment of acetylcysteine—The efficacy of acetylcysteine was assessed by comparing it with the results of supportive treatment given alone to 57 similarly poisoned patients. Most of these had been admitted during 1969-73, before specific treatment became available. Comparisons were also made with 40 patients treated with intravenous cysteamine and 20 treated with intravenous methionine during 1973-6.[3] All had plasma paracetamol concentrations above the treatment line, and except for the use of specific treatment their management was similar to that in the acetylcysteine-treated group. Severe liver damage was defined as an increase in serum AST or ALT activity above 1000 IU/l and renal impairment as a rise in the plasma creatinine concentration from normal to over 300 μmol/l (3·4 mg/100 ml).

Results

Patients given supportive treatment, acetylcysteine, and cysteamine and methionine were broadly comparable in age, sex, severity of poisoning, and ingestion-admission interval (table I). More patients treated with acetylcysteine, however, had taken paracetamol with other drugs and alcohol, and there was a highly significant excess of Distalgesic poisoning in this group compared with the group given supportive treatment ($\chi^2 = 14·9$; $P < 0·001$).

LIVER DAMAGE

Acetylcysteine given within 10 hours—Only one of the 62 patients given acetylcysteine within 10 hours developed severe liver damage compared with 33 (58%) of the 57 patients given supportive treatment.

TABLE I—*Details of patients with severe paracetamol poisoning given supportive treatment, cysteamine and methionine, and acetylcysteine*

	Supportive treatment	Cysteamine and methionine	Acetylcysteine
No of patients	57	60	100
Mean age in years (range)	30 (16-73)	28 (14-71)	33 (13-82)
No (%) male	20 (35)	20 (33)	42 (42)
Mean plasma paracetamol concentration on admission (mg/l)	208	267	209
Mean ingestion-admission interval (hours)	8·1	6·5	8·4
No (%) at high risk*	28 (49)	38 (63)	60 (60)
No (%) also taking alcohol	16 (28)	18 (30)	41 (41)
No (%) also taking other drugs	19 (33)	21 (35)	52 (52)
No (%) taking Distalgesic	2 (4)	10 (17)	31 (31)

*Plasma paracetamol concentration exceeding semilogarithmic plot of 300 mg/l at four hours and 45 mg/l at 15 hours.

Patients given acetylcysteine showed a minor increase in mean maximum serum ALT activity to 113 IU/l, while their mean plasma bilirubin concentration and prothrombin-time ratio were within normal limits. In contrast, the corresponding values in the patients given supportive treatment were over 2022 IU/l, 56 μmol/l (3·3 mg/100 ml), and 1·9 respectively (table II). (In this group the mean serum ALT activity was underestimated, since from 1969 to 1973 the results were often reported as over 850 or over 1000 IU/l.) Thirty-three patients given acetylcysteine (53%) and 28 given supportive treatment (49%) were high-risk cases. Acetylcysteine was almost completely effective in preventing even mild liver damage when given within eight hours of ingesting paracetamol. In 36 out of 40 patients (90%) treated within this time (mean 6·3 hours) the serum ALT activity remained normal (up to 40 IU/l), the mean maximum value being only 27 IU/l and the highest individual value 79 IU/l.

Acetylcysteine given within 10-24 hours—In 38 cases acetylcysteine was given 10-24 (mean 15) hours after ingestion. Severe liver damage occurred in 20 (53%), and the mean maximum serum ALT activity, plasma bilirubin concentration, and prothrombin-time ratio were 3814 IU/l, 57 μmol/l (3·3 mg/100 ml), and 1·9 respectively. These results were closely similar to those in the group given supportive treatment (table II), though more patients given acetylcysteine were high-risk cases (71% compared with 49%). Severe liver damage occurred in three out of nine patients treated 10-12 hours, seven out of 15 treated 12-15 hours, and 10 out of 14 treated 15-24 hours after ingestion.

High-risk patients—The efficacy of acetylcysteine is best assessed in the high-risk cases, since severe liver damage occurred in 89% of such patients given supportive treatment while the incidence in those at intermediate risk was only 28%. Table III gives the results. Of the 33 high-risk patients given acetylcysteine within 10 hours after ingestion, only one developed severe liver damage, and there was little or no disturbance of liver function in the others. Acetylcysteine was particularly effective in the 19 high-risk patients treated within eight hours: serum ALT activity remained normal in 17 (89%), and the maximum values in the other two patients were 61 and 79 IU/l. The incidences of liver damage and its severity were similar in patients given supportive treatment and those given acetylcysteine 10-24 hours after ingestion.

Critical ingestion-treatment interval for protection against liver damage—To define more precisely the critical time limit for efficacy of acetylcysteine we calculated the incidence and severity of liver damage at different ingestion-treatment intervals. Patients who presented late, however, were more severely poisoned and more often at high risk irrespective of treatment. Comparisons with the supportive-treatment group as a whole were not therefore appropriate, since most patients presented early; hence to avoid misleading conclusions we analysed separately patients at high risk and those at intermediate risk. Table IV gives the results. Severe liver damage occurred in 25 (89%) of the 28 patients given supportive treatment, and the incidence was similar in the 13 admitted within 10 hours and the 15 admitted more than 10 hours after ingestion. There was complete protection against severe liver damage when treatment with acetylcysteine was begun within eight hours, but the incidence was 7% when treatment was begun at 8-10 hours, 43% when begun at 10-12 hours, and 56% when begun at 12-15 hours. Treatment after 15 hours was ineffective, severe liver damage occurring in 82% of patients. In the intermediate-risk group there was no clear evidence of protection after 10 hours, but the numbers were small.

RENAL IMPAIRMENT

There was no renal impairment (as defined here) in patients given acetylcysteine within 10 hours (see table V). Nevertheless, renal

TABLE II—*Liver damage in patients with paracetamol poisoning given supportive treatment or intravenous acetylcysteine*

Treatment	No of patients	Mean maximum serum ALT activity (IU/l)	Mean maximum plasma bilirubin concentration (μmol/l)	Mean maximum prothrombin-time ratio	No (%) of patients with severe liver damage*	No (%) of patients at high risk†
Acetylcysteine given within 10 hours	62	113	15	1·3	1 (2)	33 (53)
Acetylcysteine given within 10-24 hours	38	3814	57	1·9	20 (53)	27 (71)
Supportive treatment	57	>2022	56	1·9	33 (58)	28 (49)

*Serum AST or ALT activity exceeding 1000 IU/l.
†Plasma paracetamol concentration exceeding semilogarithmic plot of 300 mg/l at four hours and 45 mg/l at 15 hours.
Conversion: SI to traditional units—Plasma bilirubin: 1 μmol/l ≈ 0·06 mg/100 ml.

TABLE III—*Liver damage in high-risk* patients with paracetamol poisoning given supportive treatment or intravenous acetylcysteine*

Treatment	No of patients	Mean maximum serum ALT activity (IU/l)	Mean maximum plasma bilirubin concentration (μmol/l)	Mean maximum prothrombin-time ratio	No (%) of patients with severe liver damage†
Acetylcysteine given within 10 hours	33	185	16	1·3	1 (3)
Acetylcysteine given within 10-24 hours	27	4919	72	2·1	18 (67)
Supportive treatment	28	>3186	89	2·3	25 (89)

*Plasma paracetamol concentration exceeding semilogarithmic plot of 300 mg/l at four hours and 45 mg/l at 15 hours.
†Serum AST or ALT activity exceeding 1000 IU/l.

TABLE IV—*Ingestion-treatment interval and severity of liver damage in high-risk* patients given acetylcysteine*

Ingestion-treatment interval (hours)	No of patients	Mean maximum serum ALT activity (IU/l)	Mean maximum plasma bilirubin concentration (μmol/l)	Mean maximum prothrombin-time ratio	No (%) of patients with severe liver damage†
<8	19	30	14	1·3	0
8-10	14	396	17	1·4	1 (7)
10.1.-12	7	2723	38	1·6	3 (43)
12.1-15	9	4107	59	2·0	5 (56)
15.1-24	11	6981	105	2·5	9 (82)
Supportive treatment	28	>3186	89	2·3	25 (89)

*Plasma paracetamol concentration exceeding semilogarithmic plot of 300 mg/l at four hours and 45 mg/l at 15 hours.
†Serum AST or ALT activity exceeding 1000 IU/l.

TABLE V—*Results of treatment with acetylcysteine and cysteamine and methionine in severe paracetamol poisoning*

Treatment	No of patients	No (%) at high risk*	Mean ingestion-treatment interval (hours)	No (%) of patients with severe liver damage†	No (%) of patients with renal impairment	No (%) of patients dying from hepatic failure
Acetylcysteine given within 10 hours	62	33 (53)	7·3	1 (2)	0	0
Cysteamine and methionine given within 10 hours	42	24 (57)	7·1	3 (7)	0	0
Acetylcysteine given within 10-24 hours	38	27 (71)	15·0	20 (53)	5 (13)	2 (5)
Cysteamine and methionine given within 10-24 hours	18	14 (78)	12·8	8 (44)	1 (6)	1 (6)
Supportive treatment	57	28 (49)		33 (58)	6 (11)	3 (5)

*Plasma paracetamol concentration exceeding semilogarithmic plot of 300 mg/l at four hours and 45 mg/l at 15 hours.
†Serum AST or ALT activity exceeding 1000 IU/l.

impairment occurred in 6 (11%) of the 57 patients given supportive treatment, and three required haemodialysis. Five of the 38 patients (13%) given acetylcysteine within 10-24 (mean 19·8) hours had renal impairment, of whom one required haemodialysis. Compared with supportive treatment and late acetylcysteine, the protective effect of early acetylcysteine against renal impairment was significant ($P=0·02$; Fisher's exact test).

DEATHS

None of the patients given acetylcysteine within 10 hours died from hepatic failure (see table V), but two died several days later from hypoxic brain damage and stroke after taking Distalgesic. Liver-function values remained normal in both cases. Two patients given acetylcysteine 17·8 and 24 hours after ingestion and three given supportive treatment died in hepatic coma. All were in the high-risk group. The difference in mortality from hepatic failure between patients given acetylcysteine within 10 hours and the late-treatment and supportive-treatment groups combined approached significance ($P=0·08$; one tail; Fisher's exact test).

COMPARISON WITH CYSTEAMINE AND METHIONINE

Table V compares the results of treatment with intravenous acetylcysteine and cysteamine and methionine.[5] When given within 10 hours all agents protected against severe liver damage, there were no deaths from hepatic failure, and renal impairment did not occur. Severe liver damage occurred in one of the 62 patients given acetylcysteine, none of the 27 given cysteamine, and three of the 15 given methionine, the mean maximum serum ALT activities in the three groups being 113, 149, and 1415 IU/l respectively. Serum ALT activity remained normal in 47 (76%) of the patients given acetylcysteine compared with 11 (41%) and six (40%) of those given cysteamine and methionine respectively ($\chi^2=8·7$ and 5·6; $P<0·01$ and $<0·02$). Of the high-risk patients treated within eight hours, 19 given acetylcysteine had a mean serum ALT activity of 30 IU/l compared with 222 IU/l in 12 given cysteamine and methionine ($t=2·97$; $P<0·01$). Hence acetylcysteine was apparently more effective than cysteamine and methionine. The critical ingestion-treatment interval appeared to be the same for all three compounds. The incidences of severe liver damage, fatal hepatic failure, and renal impairment were similar with supportive treatment and cysteamine, methionine, and acetylcysteine given 10-24 hours after ingestion.

SAFETY OF ACETYLCYSTEINE

Acetylcysteine did not produce any obvious side effects. Unlike cysteamine it did not cause protracted vomiting, drowsiness, irritability, and malaise. Hypokalaemia and low plasma bicarbonate concentrations were often noted during the first 72 hours, and there was a tendency towards low platelet counts, especially in patients with severe liver damage. Acetylcysteine was not responsible, however, since similar changes were observed with cysteamine, methionine, and supportive treatment. Serial ECGs often showed transient generalised T-wave flattening and prominent U waves consistent with hypokalaemia.

Discussion

Intravenous acetylcysteine was clearly highly effective in protecting against severe liver damage, renal failure, and death after paracetamol overdosage when given within 8-10 hours of ingestion. As with cysteamine and methionine, the incidence and severity of liver damage rose as the interval between

ingestion and treatment increased beyond eight hours, and treatment after 15 hours was ineffective. The importance of the critical ingestion-treatment interval is sometimes not appreciated, and conflicting claims have been made. Douglas *et al*[14] believed that cysteamine was of no definite advantage whether given before or after nine hours, while Smith *et al*[8] concluded that it might prevent further liver damage when given up to 72 hours after ingestion of paracetamol.

Our use of patients given supportive treatment as historical controls was not ideal, but to withhold specific treatment in clinical trials would be unethical. Our results suggest that in the doses used acetylcysteine is more effective than cysteamine and methionine. Methionine seemed to be the least effective. Despite administration within 10 hours, severe liver damage occurred in 20% of our patients and in 4-10% of patients given oral methionine in other studies.[7 15]

Oral acetylcysteine has been used for paracetamol poisoning in the USA,[9 10 16] but severe liver damage occurred in 17% of 49 patients treated within 10 hours despite the use of heroic doses (1330 mg/kg given over three days).[10] Acetylcysteine is apparently more effective when given intravenously than by mouth. This is not surprising, since in our experience most severely poisoned patients develop early nausea and vomiting, making oral treatment impracticable. In any event, absorption is likely to be delayed or incomplete. Frequent vomiting has been described with oral methionine,[17] and in one study vomiting apparently occurred in all 416 patients given oral acetylcysteine.[10] There seems to be no place for oral treatment of severe paracetamol poisoning when effective intravenous treatment is available.

Cysteamine invariably causes distressing side effects,[2 3 6-8 14] and methionine may be toxic.[3 7 18] Methionine is contraindicated in severe liver disease and may contribute to encephalopathy in paracetamol poisoning.[19] In contrast, acetylcysteine was noticeably free of adverse effects and on these grounds alone is preferable to cysteamine and methionine. Furthermore, acetylcysteine is readily available, and a special intravenous preparation (Parvolex, Duncan, Flockhart) is now marketed in the UK for paracetamol poisoning.

The following plan of management is proposed for paracetamol poisoning in adults. On admission blood should be taken for emergency estimation of the plasma paracetamol concentration, remembering that values obtained before four hours after ingestion may not be reliable because of the possibility of continuing absorption. Non-specific analytical methods such as those described by Wilkinson[20] and Welch and Conney[21] must not be used, since they may overestimate values by up to 700%.[22] Gastric lavage should be performed on patients admitted within four hours of ingestion and on unconscious patients.

Intravenous acetylcysteine is indicated in patients with plasma paracetamol concentrations above the treatment line, provided that treatment is started within 15 hours of ingestion. Patients who are thought to have taken over 7·5 g paracetamol more than eight hours previously, however, should be treated immediately without waiting for the plasma paracetamol result. Although treatment with acetylcysteine between 15 and 24 hours is ineffective, it probably does no harm and should not be withheld if the time of ingestion is in doubt. Severe liver damage and renal failure may occur with plasma paracetamol concentrations below the present treatment line,[5] and in view of the safety of acetylcysteine a good case can be made for lowering the line to 150 mg/l at four hours and 25 mg/l at 15 hours.

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Vancouver style

All manuscripts submitted to the *BMJ* from now on should conform to the uniform requirements for manuscripts submitted to biomedical journals (known as the Vancouver style).

The *BMJ*, together with many other international biomedical journals, has agreed to accept articles prepared in accordance with the Vancouver style and will be introducing the system from January 1980. The style (described in full in *BMJ*, 24 February, p 532) is intended to standardise requirements for authors and covers text format, presentation of methods and results, use of SI units, and the form of tables and illustrations. All the participating journals have also agreed to introduce a standard form of references.

In future references to papers submitted to the *BMJ* should include: the names of all authors if there are fewer than seven or, if there are more, the first three followed by *et al*; the title of journal articles or book chapters; the titles of journals abbreviated according to the style of *Index Medicus*; and the first and final page numbers of the article or chapter.

Examples of common forms of references are:

1 International Steering Committee of Medical Editors. Uniform requirements for manuscripts submitted to biomedical journals. *Br Med J* 1979;**1**:532-5.
2 Soter NA, Wasserman SI, Austen KF. Cold urticaria: release into the circulation of histamine and eosinophil chemotactic factor of anaphylaxis during cold challenge. *N Engl J Med* 1976;**294**:687-90.
3 Weinstein L, Swartz MN. Pathogenic properties of invading microorganisms. In: Sodeman WA Jr, Sodeman WA, eds. *Pathologic physiology: mechanisms of disease*. Philadelphia: W B Saunders, 1974:457-72.

Up to the beginning of October some 100 journals had agreed to accept articles in the Vancouver style, and a full list will be printed early in 1980.